Reviews

Polycyclic Aromatic Hydrocarbons and Cancer in Man

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Various substances and industrial processes, surrogates of exposure to polycyclic aromatic hydrocarbons (PAHs), are currently classified as human carcinogens. This paper reviews recent epidemiological studies reporting direct evidence of the carcinogenic effects of PAHs in occupationally exposed subjects. Risks of lung and bladder cancer were dose dependent when PAHs were measured quantitatively and truly nonexposed groups were chosen for comparison. These new findings suggest that the current threshold limit value of 0.2 mg/m^3 of benzene soluble matter (which indicates PAH exposure) is unacceptable because, after 40 years of exposure, it involves a relative risk of 1.2–1.4 for lung cancer and 2.2 for bladder cancer. *Key words*: bladder cancer, epidemiology, lung cancer, occupational exposure, polycyclic aromatic hydrocarbons. *Environ Health Perspect* 104:1166–1170 (1996)

According to the International Agency for Research on Cancer (IARC), soot and tar, untreated and mildly treated mineral oils, and processes used in the production of aluminum and coke or in iron and steel foundries are carcinogenic in humans. Because polycyclic aromatic hydrocarbons [PAHs; namely, hydrocarbons with three or more condensed aromatic rings in which certain carbon atoms are common to two or three rings (*1*)] are common in these occupational exposures, the findings are currently considered to be indirect evidence of the carcinogenic effects of PAHs (*2*). In recent epidemiological studies, however, occupational PAH exposure was directly estimated using either the job–exposure matrix (JEM) approach or industrial hygiene data collected in a factory. Our aim was therefore to make an appraisal of studies that report a dose–response analysis of PAH levels in relation to cancer risk and to quantify risk with respect to the current threshold limit values (TLV) fixed by the American Conference of Governmental Industrial Hygienists (ACGIH).

Methods

From January 1966 through January 1996, we traced studies in MEDLINE (National Library of Medicine, National Institutes of Health, Bethesda, MD) files under the heading polycyclic hydrocarbons. For checking purposes only, extensive research was also made from 1991 through 1996, using the following headings: aluminum workers, coke oven workers, iron foundry or steel workers, pitch and tar workers (in all the above occupations PAHs were from hot coal tar use), air pollutants, asphalt workers or roofers, carbon black, chimney sweeps, diesel exhausts, fire-fighters, machinists, mechanics, mineral oils, oil mists, petroleum industry, printing industry, road transport or railroad workers, and soot. For each heading, the heading "adverse effects" was also sought. We also searched for the following headings: pharynx or pharyngeal cancer, pancreas or pancreatic cancer, larynx or laryngeal cancer, lung cancer, kidney cancer, bladder cancer, myeloma, lymphoma, leukemia, and skin cancer. For each of these items, we also searched for "case–control" or "case–referent study."

The 10 epidemiological studies reviewed (2 cohort studies; 2 case–cohort studies, 2 case–control studies nested in cohorts, and 4 hospital- or population-based case–control studies) dealt with occupationally exposed subjects, explicitly mentioned PAH exposure and described it in quantitative or qualitative levels, and examined the carcinogenic effects of PAHs. We also selected studies in which occupational PAH exposure was mentioned but the dose–response relationship was not analyzed.

PAH levels, cancer risk estimates, and significance tests reported in the original articles are shown in Table 1. Quantitative PAH measurements were always expressed as either benzene soluble matter (BSM, mg/m^3), the benzene-soluble fraction of particulate sampled on a filter, or airborne levels of benzo(*a*)pyrene (BaP, μg/m^3). In many case–control studies, the cancer mortality risks were expressed as odds ratios (OR), which in some cases were adjusted for one confounding factor or more. When recalculated, OR was a cross-product ratio of the original frequencies. Rate ratios were calculated in two case–cohort studies. Relative risks (RR) were calculated through a comparison of cancer mortality between two subcohorts in one study. In another cohort study, the standardized incidence ratio (SIR) for cancer was obtained. The statistical test for the deviation from unity of the risk estimates was in some instances based on their 95% confidence intervals (CI). The test for the linear increase in cancer risk across the classes of increasing cumulative PAH exposure was calculated in the original papers following various methods; this was recalculated by us where necessary (one study), using the Chi-square method described by Breslow and Day (*3*).

Results

Table 1 shows dose–response analyses between levels of PAHs and the risk of lung cancer and bladder cancer. The 10 selected epidemiological studies are described below.

In 51 subjects with lung cancer and 153 controls from a cohort of 3,425 subjects who had worked in iron foundries for at least 1 year between 1918 and 1972, Tola et al. (*4*) reclassified jobs according to the BaP levels measured in 1976. Neither lung cancer OR, not adjusted for smoking (recalculated), nor the test for OR trend (recalculated) were significant; 15/51 cases (29.4%) with miscellaneous exposure were excluded.

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Spinelli et al. (5) reported the SIRs for lung cancer according to increasing levels of cumulative PAH exposure (BSM × years) in a cohort of 4213 subjects who had worked in an aluminum factory for at least 5 years in the period from 1954 (year in which the production started) through 1985. Historical BSM levels were estimated for each job, in 13 separate time intervals, on the basis of recent industrial hygiene measures and the knowledge of process modifications in the observation period. Individual exposure was the sum of products (estimated BSM concentrations per years of work) in each job. The SIRs not adjusted for smoking and the result of the test for the SIR trend were not significant for lung cancer or bladder cancer (Table 1). Furthermore, seven cases of non-Hodgkin's lymphoma were observed against the expected 6.6. The test for trend, however, was significant.

McLaughlin et al. (6) measured exposure to BaP, silica, arsenic, and radon in 338 lung cancer cases and in 1,138 controls selected from a cohort of 68,285 Chinese subjects who worked from 1972 through 1974 in iron–copper, tungsten, or tin mines or potteries. Three classes of increasing cumulative exposure to BaP were compared with one class (BaP<1.6 μg/m^3), which may have included subjects exposed to high levels of silica, arsenic, or radon. In some cases, lung cancer ORs were increased, but OR trends were never significant. Exposure to PAHs in mines, however, was too recent (early 1980s) for findings to be considered conclusive (Table 1).

In 194 lung cancer cases and in 388 controls, Jöckel et al. (7) calculated cumulative exposures to BSM, asbestos, chrome, nickel, and radon by multiplying the years of work in each occupation by a weight proportional to the corresponding level of exposure, estimated on the basis of published industrial hygiene data. Subjects with BSM × years ranging from 0 to 3 who were presumed to have had no exposure to other lung carcinogens were the reference group. Neither lung cancer ORs adjusted for smoking nor the OR trend test result were significant (Table 1).

Armstrong et al. (8) selected 338 lung cancer cases and 1,138 controls from about 16,000 subjects who had worked in an aluminum refinery plant for at least 1 year during the period 1950–1979. Exposure to BSM or BaP in these subjects was estimated by the industrial hygienists of the factory by integrating jobs with historical (5 year) average PAH levels; exposure was estimated on the basis of sparse measurements carried out from 1970. Cumulative exposure was the sum of products (years of exposure per PAH level) in each job. Reference workers were exposed to less than 1 mg/m^3 × years of BSM, or less than 10 μg/m^3 × years of BaP. Table 1, in which the lung cancer rate ratios are adjusted for smoking, shows a significant trend test. Two mathematical models, linear and nonlinear, were fitted to the data. According to the mathematical model expressing the association between lung cancer risk and cumulative BSM exposure, after controlling for the effect of smoking, the risk in a subject exposed for 40 years to 0.2 mg/m^3 of BSM (current ACGIH-TLV) is 1.25 (linear model) or 1.42 (nonlinear model), with respect to nonexposed subjects (8).

In their population-based case–control study, Nadon et al. (9) collected data on occupation and other risk factors in 3,750 patients with cancer in 14 sites and in 533 controls. The cases of cancer in a particular site were compared with the controls and with cases of other-site cancers. By means of a JEM, the subjects exposed to BaP or a source of PAH (combustion of coal, oil, wood, other, and all sources) were subdivided into three groups: nonexposed, exposed to low levels, and exposed to high levels of PAH. Subjects not exposed to a particular substance made up the complementary set for those exposed to the same specific substance. As shown in Table 1, none of the squamous-cell lung cancer ORs adjusted for smoking were significant. Furthermore, no significant excess of risk was found for cancer of the bladder, esophagus, stomach, colon, rectum, pancreas, prostate, kidney, skin (melanoma), or lymphatic tissue (non-Hodgkin's lymphoma).

Costantino et al. (10) compared lung cancer mortality in 5,321 coke workers with that in 10,497 non-coke workers in a large steel company. The cumulative exposure (BSM × months) was the sum of products between months in each job and corresponding daily BSM averages, measured in 1960 and estimated thereafter. The nonexposed group included subjects with cumula-

Table 1. Epidemiological studies on dose–response analysis of PAHs and lung or bladder cancer risk

Exposure	Cancer risk: Lung cancer	Cancer risk: Bladder cancer	Reference
PAHs (foundry)			(4)
Low	1.0 (4)[a]	—	
Medium	1.2 (3)	—	
High	1.9 (29)	—	
BSM (mg/m^3 × years) (aluminum factory)			(5)
<1	0.7 (11)	1.0 (4)	
1–4.9	1.0 (9)	0.4 (1)	
5–9.9	1.1 (7)	1.3 (2)	
10–19.9	1.2 (7)	5.0 (9)[b]	
>20	1.4 (3)	—	
BaP (μg/m^3 × years) (tin mine)			(6)
1.6–108	2.0 (23)	—	
108–250	2.7 (32)[b]	—	
>250	1.8 (17)	—	
BSM (mg/m^3 × years) (various occupations)			(7)
3–15	1.0 (18)	—	
15–40	0.7 (9)	—	
>40	1.4 (2)	—	
BSM (mg/m^3 × years) (aluminum factory)			(8)
1–9.9	1.2 (123)	—	
10–19.9	2.3 (54)[b]	—	
20–29.9	1.9 (42)[b]	—	
>30	2.1 (37)[b]	—	
BaP (μg/m^3 × years)			(8)
10–99	1.5 (94)	—	
100–199	2.2 (41)[b]	—	
200–299	2.1 (46)[b]	—	
>300	1.9 (19)[b]	—	

Exposure	Cancer risk: Lung cancer	Cancer risk: Bladder cancer	Reference
PAHs (petroleum)			(9)
Low	1.3 (178)[b]	0.8 (200)	
High	1.2 (85)	1.0 (94)	
BSM (mg/m^3 × months) (coke oven)			(10)
0–199	1.6 (43)[b]	—	
200–349	1.9 (56)[b]	—	
350–499	2.0 (39)[b]	—	
500–649	2.7 (27)[b]	—	
>650	3.1 (56)[b]	—	
PAHs			(11)
Medium aromatic amines			
Possible	—	1.2 (21)	
Definite	—	2.4 (11)[b]	
High aromatic amines			
Possible	—	3.8 (37)[b]	
Definite	—	4.8 (2)	
PAHs (various occupations)			(12)
Low	—	1.2 (127)	
Medium	—	1.4 (64)	
High	—	1.8 (26)	
BSM (mg/m^3 × years) (aluminum factory)			(13)
1.0–9.9	—	1.7 (32)	
10–19.9	—	3.9 (23)[b]	
20–29.9	—	7.3 (35)[b]	
>30	—	5.2 (26)[b]	
BaP (μg/m^3 × years) (aluminum factory)			(13)
10–99.9	—	2.0 (29)[b]	
100–199.9	—	6.2 (26)[b]	
200–299.9	—	6.7 (30)[b]	
>300	—	4.4 (18)[b]	

BSM, benzene soluble matter; BaP, benzo(*a*)pyrene.
[a]The number of exposed cases is shown in parentheses.
[b]$p<0.05$.

tive BSM exposure equal to 0. For overall lung cancer, RR =1.95; 95% CI, 1.6–2.3. Moreover, as shown in Table 1, many RRs were significantly raised; the result of the test for the RR trend was significant. Information on smoking habits were not available. A significant excess for prostate cancer was also reported, but the test for RR trend across the classes of cumulative BSM exposure was not significant.

Bonassi et al. (*11*) carried out a population-based case–control study in an area with a high density of chemical plants. The levels of occupational exposure to both PAHs and aromatic amines (AA) were ascertained by means of a JEM in 150 bladder cancer cases and 450 age-matched controls. The reference group had no exposure to PAHs, AAs, or other occupational carcinogens. As shown in Table 1, in each AA exposure level the age-smoking adjusted ORs for definite exposure are twofold that for possible PAH exposure.

Clavel et al. (*12*) built a semiquantitative index of PAH exposure by means of a JEM applied to occupational data collected through questionnaires in 765 cases of bladder cancer and 765 controls. None of the bladder cancer risks (Table 1) adjusted for smoking, coffee consumption, and occupational exposure to AA were significant, although the OR trend was significant.

In 138 cases of bladder cancer and 414 controls selected from the same cohort of aluminum workers described by Armstrong et al. (*8*), Tremblay et al. (*13*) reported a significant increase of smoking adjusted RRs with increasing cumulative BSM (or BaP) exposure (Table 1). A linear model (1+bx) was fitted, and it expressed the association between cumulative BSM exposure and bladder cancer risk; lagging 10 years before the diagnosis, the mathematical model (RR = 1 + 0.1521 × mg/m^3-years BSM) predicts that the risk of bladder cancer is 2.2 times higher in subjects exposed to 0.2 mg/m^3 BSM (current ACGIH-TLV value) for 40 years than in nonexposed workers. The estimate is not confounded by smoking (*13*).

In the 1980s, IARC reviewed numerous epidemiological studies on PAH-exposed workers whose occupational exposure was assessed on the basis of job title or industrial process involved. Given the long latency between first exposure and cancer, these workers were exposed mainly during the first half of the century, when data on industrial hygiene were scarce. A definite risk of cancer was found in workers employed in the coke (lung cancer), aluminum (lung and bladder cancer), and steel industries (lung cancer), which were subsequently considered Group 1 carcinogens (*14*) together with coal-tar pitches (*15*), untreated and mildly treated mineral oils (*16*), and soots (*15*) (Table 2). On the other hand, inconsistencies between studies, lack of control of confounding factors, potential bias, and uncertainty regarding a dose–response relationship precluded any definitive conclusions for other occupations: roofers and asphalt workers (*15*); mechanics exposed to engine exhaust; and bus and truck drivers, railroad workers, and operators of excavating machines exposed to diesel exhaust in mines and tunnels (*17*).

Table 2. Epidemiological and experimental evidence on the carcinogenicity of industrial processes, complex mixtures involving exposure to PAHs, and single PAHs according to IARC

Process or substance	Epidemiological evidence	Experimental evidence	IARC Group[a]	Reference
Industrial processes				
Aluminum production	Sufficient	—	1	(*14*)
Coal gasification	Sufficient	—	1	(*14*)
Coke production	Sufficient	—	1	(*14*)
Iron and steel founding	Sufficient	—	1	(*14*)
Complex mixtures				
Bitumens (extracts)	—	Sufficient	2B	(*15*)
Carbon black	Inadequate	Sufficient	2B	(*16*)
Coal tars	Sufficient	Limited	1	(*15*)
Diesel engine exhaust	Limited	Sufficient	2A	(*17*)
Engine exhaust, gasoline	Inadequate	Sufficient	2B	(*17*)
Mineral oils, untreated/mildly treated	Sufficient	Sufficient	1	(*16*)
Shale oils	Sufficient	Sufficient	1	(*15*)
Soots	Sufficient	Inadequate	1	(*15*)
Substances				
Benz(*a*)anthracene	—	Sufficient	2A	(*2*)
Benzo(*b*)fluoranthene	—	Sufficient	2B	(*2*)
Benzo(*j*)fluoranthene	—	Sufficient	2B	(*2*)
Benzo(*k*)fluoranthene	—	Sufficient	2B	(*2*)
Benzo(*a*)pyrene	—	Sufficient	2A	(*2*)
Chrysene	—	Sufficient	2B	(*2*)
Dibenz(*a,h*)acridine	—	Sufficient	2B	(*2*)
Dibenz(*a,j*)acridine	—	Sufficient	2B	(*2*)
Dibenz(*a,h*)anthracene	—	Sufficient	2A	(*2*)
7H-Dibenz(*c,g*)carbazole	—	Sufficient	2B	(*2*)
Dibenzo(*a,e*)pyrene	—	Sufficient	2B	(*2*)
Dibenzo(*a,h*)pyrene	—	Sufficient	2B	(*2*)
Dibenzo(*a,i*)pyrene	—	Sufficient	2B	(*2*)
Dibenzo(*a,l*)pyrene	—	Sufficient	2B	(*2*)
Indeno(1,2,3-*cd*)pyrene	—	Sufficient	2B	(*2*)

[a]Group 1, definite carcinogen; Group 2A, probable carcinogen; and Group 2B, possible human carcinogen.

In two recent reviews, moreover, the available epidemiological evidence was found to be insufficient for definitively establishing that diesel engine exhaust (containing low levels of PAHs) is a lung or laryngeal carcinogen in humans (*18,19*). In another recent review in which an aggregated analysis of epidemiological studies was made, no significant lung cancer risk excess was found in road pavers exposed mainly to asphalt (which mainly comes from distillation of petroleum and is poor in PAHs), whereas roofers, who were exposed to both asphalt and coal tar, were found to be at risk for lung and stomach cancer (*20*).

No experimental evidence of carcinogenicity was available for any of the above industrial processes and exposure circumstances. By contrast, several PAHs were identified as carcinogens in numerous studies on animals (*2*). However, because PAHs always occur as mixtures, the experimental findings were not supported by epidemiological evidence. These substances were therefore scored by IARC as probable (Group 2A) or possible (Group 2B) human carcinogens (Table 2).

Discussion

Until the 10 recent epidemiological studies reviewed here (published about 200 years after Pott's initial finding of scrotal cancer in chimney sweeps) (*4–13*), no direct epidemiological evidence of an association between occupational PAH exposure and cancer had been reported in man. Greenland (*21*) pointed out that the pooling of risk estimates from multiple studies should be undertaken based on the assumption that the only source of variability between studies is sampling variability. The risk estimates in the studies reported in this review, however, are not the outcome of a single hazard, but of a large collection of exposures that vary depending on chemical mixture, intensity, and duration. Therefore, as the available effect estimates cannot be

considered unbiased estimators of a single true effect, they were not pooled.

Boffetta et al. (*22*) suggested that the main difficulties in quantifying risk in the study of weak associations are a lack of quantitative information on the level of exposure (dilution of true risk estimates could be due to pooling of findings from quantitatively different exposure experiences) and difficulty in identifying a truly nonexposed comparison group. A common error in many case–control studies, particularly when many exposures are evaluated, is to compare each exposed group (ever exposed to a substance) with the complementary set of nonexposed (never exposed to the substance under study) subjects, instead of with a group without any exposure. The OR may be underestimated because the reference category may include occupations at a high risk of cancer (*23*).

The JEM approach is a qualitative method that, on the basis of a specific hypothesis *a priori*, approximates categories of exposure and cannot replace real measurements of occupational exposure because of time changes in level of exposure in an occupation, changes in type of exposure introduced by technology, and different exposures that might coexist in a same professional category and even within a single job. Cohort studies on workers exposed to specific agents are a better approach, particularly when historical data on exposure are available. In these studies, however, information on smoking is almost always unavailable. The case–control study nested in a cohort, in which information on confounding factors is obtained and the risk estimates are controlled, is considered the most accurate and efficient method available for the evaluation of occupational risks (*23*).

It may therefore be concluded that the studies reviewed should be listed according to their validity. The findings of Nadon et al. (*9*) appear to be the least reliable because of both the lack of quantitative data on PAH exposure and the choice of the complementary set of subjects not exposed to a particular substance as a reference group. We recalculated ORs for cancer in various sites using subjects not exposed to all the PAH sources as a reference group; we found these ORs to be systematically greater than those reported in the original work. Misclassification of exposure therefore resulted in a marked OR underestimation. Likewise, in the study of Jöckel et al. (*7*), PAH levels were qualitative and the reference group may have included subjects exposed to other pulmonary carcinogens. In the case–control study nested in a cohort (*6*), data on quantitative BaP were reported but, as exposure was too recent, they were not of etiologic significance. Moreover, the group of subjects not exposed to PAHs possibly included those exposed to high levels of radon, arsenic, or silica. Despite the lack of industrial hygiene measures, the studies made by Bonassi et al. (*11*) and Clavel et al. (*12*) appear more reliable because their reference groups did not include subjects exposed to bladder carcinogens, in particular to AAs. In the study of Tola et al. (*4*), exposures to BaP were measured, but they were too recent (1976) with respect to the period of cohort selection (1918–1972). There are further difficulties: 29% of the cases were not classified for exposure, and smoking data were not provided. The precision of risk estimates was poor in the study of Spinelli et al. (*5*), given the small number of lung cancer cases observed particularly in the top level of BSM dose; information on smoking habits was not available. In Costantino et al. (*10*), historical measurements of airborne PAHs were made and a larger number of cases were investigated; although data on smoking were not given, the trend toward increasing risk with increasing dose may be considered, according to Steenland et al. (*24*), to be confirmation of a true association instead of a spurious one due to smoking. Finally, the more accurate studies are those made by Armstrong et al. (*8*) and Tremblay et al. (*13*), who reported historical quantitative data on exposure to PAHs (according to which the nonexposed group was chosen) and gave information on smoking habits (with risk estimates adjusted accordingly).

In the aluminum factory workers studied by Tremblay et al. (*13*) and Armstrong et al. (*8*), airborne 2-naphthylamine (TWA, <1 to 410 ng/m^3) and nitro-arenes were also found; the latter may be transformed through enzymatic reduction in aryl-amines, which are also bladder carcinogens. In aluminum workers, unlike in smokers (*25*), the risk of bladder cancer is higher than that of lung cancer. According to Bonassi et al. (*11*) and Clavel et al. (*12*), this may be explained on the basis of the assumption that PAHs and AAs have an independent and additive carcinogenic effect on the bladder epithelium. If the risk of bladder cancer is attributed to the AAs alone, and given that lung cancer excess was not confirmed by Spinelli et al. (*5*), McLaughlin et al. (*6*), or Tola et al. (*4*), PAHs may not be carcinogens at all. But this hypothesis is contradicted by Costantino et al. (*10*) and Armstrong et al. (*8*). Furthermore, as stated above, the findings reported by Spinelli (*5*), McLaughlin (*6*), and Tola (*4*) are less valid than those of Armstrong (*8*) and Costantino (*10*).

It has been suggested that in reviewing studies with a dose–response analysis, a publication bias may occur because authors tend to report only positive results in detail (*20*). However, other studies without a dose–response analysis always reported significant associations. A nested case–control study clearly suggested that the excess of lung cancer in a foundry was attributable to exposure to PAHs in the production of ferro-chrome (*26*). In a population-based case–control study, the RR of lung cancer adjusted for smoking was 1.6 for occupational exposure to PAHs, 1.9 for the exposure to asbestos, and 3.3 for joint exposure to PAHs and asbestos (*27*). Finally, it was reported that exposure to PAHs probably caused lung cancer in a nickel–copper refinery (*28*).

In conclusion, the more accurate recent studies, which reveal an increase in lung and bladder cancer with the occupational exposure to PAHs, support the earlier findings provided by the qualitative job title-based epidemiological studies. In the past, however, there were high levels of carcinogens in many occupational settings, whereas in industrialized countries, the current exposures are generally near to background level (*29*). A quantitative estimate of exposure may therefore prevent a dilution of effects and a subsequent underestimation of cancer risk in epidemiological studies. Furthermore, it has been pointed out that occupational diseases are caused by exposures, not jobs (*30*). Industrial and occupational categories, often inaccurate surrogates of exposure, were excluded from the list of carcinogens in the Finnish registry of occupational exposure to carcinogens, where only workers exposed to carcinogens above background levels (e.g., BaP >0.1 μg/m^3) were reported (*31*). On the other hand, quantification of exposure may be important in decisional criteria used in compensating cancer victims among occupationally exposed subjects, as recently shown by Armstrong and Thériault in aluminum workers (*32*). Measurement of exposure may also help policy makers and occupational hygienists. For example, the TLV for PAHs was established in 1967 when the ACGIH adopted the TLV of 0.2 mg/m^3 for BSM, yet it has not been modified since then (*33*). The results reviewed here suggest that this value should be lowered. The lowering of PAHs would be accompanied by a proportional lowering of AA levels, with reduced risk of cancer of both bladder and lung in the aluminum industry and elsewhere.

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